DURAGESIC- fentanyl patch
Janssen Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DURAGESIC® safely and effectively. See full prescribing information for DURAGESIC.

DURAGESIC (Fentanyl Transdermal System) for transdermal administration, CII
Initial U.S. Approval: 1968

WARNING: ADDICTION, ABUSE, and MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION, and EXPOSURE TO HEAT

See full prescribing information for complete boxed warning.

- **DURAGESIC exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing, and monitor regularly for development of these behaviors or conditions. (5.1)**
- **Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. (5.2)**
- **Accidental exposure to DURAGESIC, especially in children, can result in fatal overdose of fentanyl. (5.3)**
- **Prolonged use of DURAGESIC during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available. (5.4)**
- **Initiation of CYP 3A4 inhibitors (or discontinuation of CYP 3A4 inducers) can result in a fatal overdose of fentanyl from DURAGESIC. (5.10)**
- **Avoid exposing the DURAGESIC application site and surrounding area to direct external heat sources. Temperature dependent increases in fentanyl release from the system may result in overdose and death. (5.11)**

RECENT MAJOR CHANGES

Boxed Warning	04/2014
Indications and Usage (1)	04/2014
Dosage and Administration (2)	04/2014
Warnings and Precautions (5)	04/2014

INDICATIONS AND USAGE

- DURAGESIC is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. (1)
- Patients considered opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid. (1)

Limitations of use:

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve DURAGESIC for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. (1)

DOSAGE AND ADMINISTRATION

- For use in opioid-tolerant patients only.
- Initial dose selection: consult conversion instructions. (2.1)
- Each transdermal system is intended to be worn for 72 hours. (2.2)
- Adhere to instructions concerning administration and disposal of DURAGESIC. (2.4)
- Reduce the dose with hepatic, and renal impairment. (2.1)

DOSAGE FORMS AND STRENGTHS

Transdermal system: 12 mcg/h, 25 mcg/h, 50 mcg/h, 75 mcg/h, 100 mcg/h. (3)

CONTRAINDICATIONS

- Opioid non-tolerant patients. (4)
- Acute or intermittent pain, postoperative pain, mild pain. (4)
- Respiratory compromise, acute or severe asthma. (4)
- Paralytic ileus. (4)
- Known hypersensitivity to fentanyl or any of the components of the transdermal system. (4)

WARNINGS AND PRECAUTIONS

- Interactions with CNS depressants: Concomitant use may cause profound sedation, respiratory depression, and death. If co-administration is required, consider dose reduction of one or both drugs because of pharmacological effects. (5.5)
- Elderly, cachectic, debilitated patients, and those with chronic pulmonary disease: Monitor closely because of increased risk for life-threatening respiratory depression. (5.6, 5.7)
- Hypotensive effects: Monitor during dose initiation and titration. (5.9)
- Patients with head injury or increased intracranial pressure: Monitor for sedation and respiratory depression. Avoid use of DURAGESIC in patients with impaired consciousness or coma susceptible to intracranial effects of CO2 retention. (5.8)
- Bradycardia. Administer with caution to patients with bradyarrhythmias. (5.13)

ADVERSE REACTIONS

Most common adverse reactions (≥5%) are nausea, vomiting, somnolence, dizziness, insomnia, constipation, hyperhidrosis, fatigue, feeling cold, anorexia, headache, and diarrhea. (6.)

To report SUSPECTED ADVERSE REACTIONS, call 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Mixed agonist/antagonist and partial agonist opioid analgesics: Avoid use with DURAGESIC because they may reduce analgesic effect of DURAGESIC or precipitate withdrawal symptoms. (5.1, 7. 4)
- Monoamine oxidase inhibitors (MAOIs): Avoid DURAGESIC in patients taking MAOIs or within 14 days of stopping such treatment. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm. (8.1)
- Nursing Mothers: Breast-feeding is not advised in mothers treated with DURAGESIC. (8.3)
- Pediatric Use: Safety and efficacy in pediatric patients below the age of 2 years have not been established. To guard against accidental ingestion by children, use caution when choosing the application site for DURAGESIC. (8.4)
- Geriatric Use: Administer DURAGESIC with caution, and in reduced dosages in elderly patients. (8.5)
- Hepatic or Renal Impairment: Administer DURAGESIC with caution. Monitor for signs of fentanyl toxicity and reduce dosage, if necessary. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL EXPOSURE; NEONATAL OPIOID WITHDRAWAL SYNDROME; CYTOCHROME P450 3A4 INTERACTION; and EXPOSURE TO HEAT

Addiction, Abuse, and Misuse

DURAGESIC exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing DURAGESIC, and monitor all patients regularly for the development of these behaviors or conditions *[see Warnings and Precautions (5.1)]*.

Life-threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of DURAGESIC, even when used as recommended. Monitor for respiratory depression, especially during initiation of DURAGESIC or following a dose increase. Because of the risk of respiratory depression, DURAGESIC is contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain *[see Contraindications (4)* and *Warnings and Precautions (5.2)]*.

Accidental Exposure

Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to DURAGESIC. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure *[see Warnings and Precautions (5.3)]*.

Neonatal Opioid Withdrawal Syndrome

Prolonged use of DURAGESIC during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.4)]*.

Cytochrome P450 3A4 Interaction

The concomitant use of DURAGESIC with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving DURAGESIC and any CYP3A4 inhibitor or inducer *[see Warnings and Precautions (5.10)* and *Clinical Pharmacology (12.3)]*.

Exposure To Heat

Exposure of the DURAGESIC application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl and death *[see Warnings and Precautions (5.11)]*. Patients wearing DURAGESIC systems who develop fever or increased core body temperature due to strenuous exertion are also at risk for increased fentanyl exposure and may require an adjustment in the dose of DURAGESIC to avoid overdose and death *[see Warnings and Precautions (5.12)]*.

1 INDICATIONS AND USAGE

DURAGESIC is indicated for the management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Patients considered opioid-tolerant are those who are taking, for one week or longer, at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily, or an equianalgesic dose of another opioid.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve DURAGESIC for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

2 DOSAGE AND ADMINISTRATION

2.1 Initial Dosing

DURAGESIC should be prescribed only by healthcare professionals who are knowledgeable in the use of potent opioids for the management of chronic pain.

Due to the risk of respiratory depression, DURAGESIC is only indicated for use in patients who are already opioid-tolerant. Discontinue or taper all other extended-release opioids when beginning DURAGESIC therapy. As DURAGESIC is only for use in opioid-tolerant patients, do not begin any patient on DURAGESIC as the first opioid.

Patients considered opioid-tolerant are those who are taking at least 60 mg of morphine daily, or at least 30 mg of oral oxycodone daily, or at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Initiate the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse, and misuse *[see Warnings and Precautions (5.1)]*. Monitor patients closely for respiratory depression, especially within the first 24–72 hours of initiating therapy with DURAGESIC when serum concentrations from the initial patch will peak *[see Warnings and Precautions (5.2)]*.

The recommended starting dose when converting from other opioids to DURAGESIC is intended to minimize the potential for overdosing patients with the first dose.

Discontinue all other around-the-clock opioid drugs when DURAGESIC therapy is initiated.

While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products. As such, it is preferable to underestimate a patient's 24-hour fentanyl requirements and provide rescue medication (e.g., immediate-release opioid) than to overestimate the 24-hour fentanyl requirements which could result in adverse reactions. In a DURAGESIC clinical trial, patients were converted from their prior opioid to DURAGESIC using Table 1 as a guide for the initial DURAGESIC dose.

Consider the following when using the information in Table 1:

- This is **not** a table of equianalgesic doses.
- The conversion doses in this table are only for the conversion **from** one of the listed oral or parenteral opioid analgesics **to** DURAGESIC.
- The table **cannot** be used to convert **from** DURAGESIC **to** another opioid. Doing so will result in an overestimation of the dose of the new opioid and may result in fatal overdose.

To convert patients from oral or parenteral opioids to DURAGESIC, use Table 1. **Do not use Table 1 to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative and will overestimate the dose of the new agent.**

Table 1*: DOSE CONVERSION TO DURAGESIC

Current Analgesic	Daily Dosage (mg/day)			
Oral morphine	60–134	135–224	225–314	315–404
Intramuscular or Intravenous morphine	10–22	23–37	38–52	53–67
Oral oxycodone	30–67	67.5–112	112.5–157	157.5–202
Oral codeine	150–447			
Oral hydromorphone	8–17	17.1–28	28.1–39	39.1–51
Intravenous hydromorphone	1.5–3.4	3.5–5.6	5.7–7.9	8–10
Intramuscular meperidine	75–165	166–278	279–390	391–503
Oral methadone	20–44	45–74	75–104	105–134
	□	□	□	□
Recommended DURAGESIC Dose	25 mcg/hour	50 mcg/hour	75 mcg/hour	100 mcg/hour

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table 1, use the conversion methodology outlined above with Table 2.

* Table 1 should not be used to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative. Use of Table 1 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible *[see Dosage and Administration (2.3)]*.

Alternatively, for adult and pediatric patients taking opioids or doses not listed in Table 1, use the following methodology:

1. Calculate the previous 24-hour analgesic requirement.
2. Convert this amount to the equianalgesic oral morphine dose using a reliable reference.

Refer to Table 2 for the range of 24-hour oral morphine doses that are recommended for conversion to each DURAGESIC dose. Use this table to find the calculated 24-hour morphine dose and the corresponding DURAGESIC dose. Initiate DURAGESIC treatment using the recommended dose and titrate patients upwards (no more frequently than 3 days after the initial dose and every 6 days thereafter) until analgesic efficacy is attained.

3. **Do not use Table 2 to convert from DURAGESIC to other therapies** because this conversion to DURAGESIC is conservative and will overestimate the dose of the new agent.

Table 2*: RECOMMENDED INITIAL DURAGESIC DOSE BASED UPON DAILY ORAL MORPHINE DOSE

Oral 24-hour Morphine (mg/day)	DURAGESIC Dose (mcg/hour)
60–134	25
135–224	50
225–314	75

315–404	100
405–494	125
495–584	150
585–674	175
675–764	200
765–854	225
855–944	250
945–1034	275
1035–1124	300

NOTE: In clinical trials, these ranges of daily oral morphine doses were used as a basis for conversion to DURAGESIC.

* Table 2 should not be used to convert from DURAGESIC to other therapies because this conversion to DURAGESIC is conservative. Use of Table 2 for conversion to other analgesic therapies can overestimate the dose of the new agent. Overdosage of the new analgesic agent is possible *[see Dosage and Administration (2.5)]*.

For delivery rates in excess of 100 mcg/hour, multiple systems may be used.

Hepatic Impairment

Avoid the use of DURAGESIC in patients with severe hepatic impairment. In patients with mild to moderate hepatic impairment, start with one half of the usual dosage of DURAGESIC. Closely monitor for signs of sedation and respiratory depression, including at each dosage increase *[see Warnings and Precautions (5.14), Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

Renal Impairment

Avoid the use of DURAGESIC in patients with severe renal impairment. In patients with mild to moderate renal impairment, start with one half of the usual dosage of DURAGESIC. Closely monitor for signs of sedation and respiratory depression, including at each dosage increase *[see Warnings and Precautions (5.15), Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)]*.

2.2 Titration and Maintenance of Therapy

Individually titrate DURAGESIC to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving DURAGESIC to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or misuse. Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration. During chronic therapy, periodically reassess the continued need for opioid analgesics.

The dosing interval for DURAGESIC is 72 hours. Do not increase the DURAGESIC dose for the first time until at least 3 days after the initial application. Titrate the dose based on the daily dose of supplemental opioid analgesics required by the patient on the second or third day of the initial application.

It may take up to 6 days for fentanyl levels to reach equilibrium on a new dose *[see Clinical Pharmacology (12.3)]*. Therefore, evaluate patients for further titration after no less than two 3-day applications before any further increase in dosage is made.

Base dosage increments on the daily dosage of supplementary opioids, using the ratio of 45 mg/24 hours of oral morphine to a 12 mcg/hour increase in DURAGESIC dose.

If unacceptable opioid-related adverse reactions are observed, the subsequent doses may be reduced. Adjust the dose to obtain an appropriate balance between management of pain and opioid-related adverse

reactions.

A small proportion of adult patients may not achieve adequate analgesia using a 72-hour dosing interval and may require systems to be applied at 48 hours rather than at 72 hours, only if adequate pain control cannot be achieved using a 72-hour regimen. An increase in the DURAGESIC dose should be evaluated before changing dosing intervals in order to maintain patients on a 72-hour regimen.

Dosing intervals less than every 72 hours were not studied in children and adolescents and are not recommended.

2.3 Administration of DURAGESIC

DURAGESIC patches are for transdermal use, only.

Proper handling of DURAGESIC is necessary in order to prevent serious adverse outcomes, including death, associated with accidental secondary exposure to DURAGESIC *[see Warnings and Precautions (5.3)].*

Application and Handling Instructions

- Patients should apply DURAGESIC to intact, non-irritated, and non-irradiated skin on a flat surface such as the chest, back, flank, or upper arm. In young children and persons with cognitive impairment, adhesion should be monitored and the upper back is the preferred location to minimize the potential of inappropriate patch removal. Hair at the application site may be clipped (not shaved) prior to system application. If the site of DURAGESIC application must be cleansed prior to application of the patch, do so with clear water. Do not use soaps, oils, lotions, alcohol, or any other agents that might irritate the skin or alter its characteristics. Allow the skin to dry completely prior to patch application.
- Patients should apply DURAGESIC immediately upon removal from the sealed package. The patch must not be altered (e.g., cut) in any way prior to application. DURAGESIC should not be used if the pouch seal is broken or if the patch is cut or damaged.
- The transdermal system is pressed firmly in place with the palm of the hand for 30 seconds, making sure the contact is complete, especially around the edges.
- Each DURAGESIC patch may be worn continuously for 72 hours. The next patch is applied to a different skin site after removal of the previous transdermal system.
- If problems with adhesion of the DURAGESIC patch occur, the edges of the patch may be taped with first aid tape. If problems with adhesion persist, the patch may be overlayed with a transparent adhesive film dressing.
- If the patch falls off before 72 hours, dispose of it by folding in half and flushing down the toilet. A new patch may be applied to a different skin site.
- Patients (or caregivers who apply DURAGESIC) should wash their hands immediately with soap and water after applying DURAGESIC.
- Contact with unwashed or unclothed application sites can result in secondary exposure to DURAGESIC and should be avoided. Examples of accidental exposure include transfer of a DURAGESIC patch from an adult's body to a child while hugging, sharing the same bed as the patient, accidental sitting on a patch and possible accidental exposure of a caregiver's skin to the medication in the patch while applying or removing the patch.
- Instruct patients, family members, and caregivers to keep patches in a secure location out of the reach of children and of others for whom DURAGESIC was not prescribed.

Avoidance of Heat

Instruct patients to avoid exposing the DURAGESIC application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds, while wearing the system *[see Warnings and Precautions (5. 11)]*.

2.4 Disposal Instructions

Failure to properly dispose of DURAGESIC has resulted in accidental exposures and deaths *[see Warnings and Precautions (5.3)]*.

Patients should dispose of used patches immediately upon removal by folding the adhesive side of the patch to itself, then flushing down the toilet.

Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Patients should dispose of any patches remaining from a prescription as soon as they are no longer needed.

2.5 Discontinuation of DURAGESIC

Significant amounts of fentanyl continue to be absorbed from the skin for 24 hours or more after the patch is removed *[see Clinical Pharmacology (12.3)]*.

To convert patients to another opioid, remove DURAGESIC and titrate the dose of the new analgesic based upon the patient's report of pain until adequate analgesia has been attained. Upon system removal, 17 hours or more are required for a 50% decrease in serum fentanyl concentrations. Withdrawal symptoms are possible in some patients after conversion or dose adjustment *[see Warnings and Precautions (5.17)]*.

Do not use Tables 1 and 2 to convert from DURAGESIC to other therapies to avoid overestimating the dose of the new agent resulting in overdose of the new analgesic and possibly death.

When discontinuing DURAGESIC and not converting to another opioid, use a gradual downward titration, such as halving the dose every 6 days, in order to reduce the possibility of withdrawal symptoms *[see Warnings and Precautions (5.17)]*. It is not known at what dose level DURAGESIC may be discontinued without producing the signs and symptoms of opioid withdrawal.

3 DOSAGE FORMS AND STRENGTHS

DURAGESIC is available as:

- DURAGESIC 12 mcg/hour[1] Transdermal System (system size 5.25 cm^2).
- DURAGESIC 25 mcg/hour Transdermal System (system size 10.5 cm^2).
- DURAGESIC 50 mcg/hour Transdermal System (system size 21 cm^2).
- DURAGESIC 75 mcg/hour Transdermal System (system size 31.5 cm^2).
- DURAGESIC 100 mcg/hour Transdermal System (system size 42 cm^2).

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1 This lowest dosage is designated as 12 mcg/hour (however, the actual dosage is 12.5 mcg/hour) to distinguish it from a 125 mcg/h dosage that could be prescribed by multiple patches.

4 CONTRAINDICATIONS

DURAGESIC is contraindicated in the following patients and situations:

- in patients who are not opioid-tolerant.
- in the management of acute or intermittent pain, or in patients who require opioid analgesia for a short period of time.
- in the management of post-operative pain, including use after out-patient or day surgeries, (e.g., tonsillectomies).
- in the management of mild pain.
- in patients with significant respiratory compromise, especially if adequate monitoring and resuscitative equipment are not readily available.

- in patients who have acute or severe bronchial asthma.
- in patients who have or are suspected of having paralytic ileus.
- in patients with known hypersensitivity to fentanyl or any components of the transdermal system. Severe hypersensitivity reactions, including anaphylaxis have been observed with DURAGESIC *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Addiction, Abuse, and Misuse

DURAGESIC contains fentanyl, an opioid agonist and a Schedule II controlled substance. As an opioid, DURAGESIC exposes users to the risks of addiction, abuse, and misuse *[see Drug Abuse and Dependence (9)]*. As modified-release products such as DURAGESIC deliver the opioid over an extended period of time, there is a greater risk for overdose and death due to the larger amount of fentanyl present.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed DURAGESIC and in those who obtain the drug illicitly. Addiction can occur at recommended doses and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing DURAGESIC, and monitor all patients receiving DURAGESIC for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol addiction or abuse) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the prescribing of DURAGESIC for the proper management of pain in any given patient. Patients at increased risk may be prescribed modified-release opioid formulations such as DURAGESIC, but use in such patients necessitates intensive counseling about the risks and proper use of DURAGESIC along with intensive monitoring for signs of addiction, abuse, and misuse.

Abuse or misuse of DURAGESIC by placing it in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking, overdose, and death *[see Overdosage (10)]*.

Opioid agonists such as DURAGESIC are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing DURAGESIC. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused drug *[see Patient Counseling Information (17)]*. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.2 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression from opioid use, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status *[see Overdosage (10)]*. Carbon dioxide (CO_2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

DURAGESIC is indicated only in opioid tolerant patients because of the risk for respiratory depression and death. While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of DURAGESIC, the risk is greatest during the initiation of therapy or following a dose increase. Closely monitor patients for respiratory depression when initiating therapy with DURAGESIC.

To reduce the risk of respiratory depression, proper dosing and titration of DURAGESIC are essential *[see Dosage and Administration (2)]*. Overestimating the DURAGESIC dose when converting patients from another opioid product can result in fatal overdose with the first dose.

Accidental exposure to DURAGESIC, especially in children, can result in respiratory depression and death due to an overdose of fentanyl.

5.3 Accidental Exposure

A considerable amount of active fentanyl remains in DURAGESIC even after use as directed. Death and other serious medical problems have occurred when children and adults were accidentally exposed to DURAGESIC. Accidental or deliberate application or ingestion by a child or adolescent will cause respiratory depression that can result in death. Placing DURAGESIC in the mouth, chewing it, swallowing it, or using it in ways other than indicated may cause choking or overdose that could result in death. Improper disposal of DURAGESIC in the trash has resulted in accidental exposures and deaths.

Advise patients about strict adherence to the recommended handling and disposal instructions in order to prevent accidental exposure to DURAGESIC *[see Dosage and Administration (2.4), (2.5)]*.

5.4 Neonatal Opioid Withdrawal Syndrome

Prolonged use of DURAGESIC during pregnancy can result in withdrawal signs in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn.

5.5 Interactions with Central Nervous System Depressants

Hypotension, profound sedation, coma, respiratory depression, and death may result if DURAGESIC is used concomitantly with alcohol or other central nervous system (CNS) depressants (e.g., sedatives, anxiolytics, hypnotics, neuroleptics, other opioids).

When considering the use of DURAGESIC in a patient taking a CNS depressant, assess the duration use of the CNS depressant and the patient's response, including the degree of tolerance that has developed to CNS depression. Additionally, evaluate the patient's use of alcohol or illicit drugs that cause CNS depression. If the decision to begin DURAGESIC is made, reduce the starting dose, monitor patients for signs of sedation and respiratory depression, and consider using a lower dose of the concomitant CNS depressant *[see Drug Interactions (7.1)]*.

5.6 Use in Elderly, Cachectic, and Debilitated Patients

Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients as they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients. Monitor such patients closely, particularly when initiating and titrating DURAGESIC and when DURAGESIC is given concomitantly with other drugs that depress respiration *[see Warnings and Precautions (5.2)]*.

5.7 Chronic Pulmonary Disease

Monitor patients with significant chronic obstructive pulmonary disease or cor pulmonale, and patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression for respiratory depression, particularly when initiating therapy with DURAGESIC, as in these patients, even usual therapeutic doses of DURAGESIC may decrease respiratory drive to the point of apnea *[see Warnings and Precautions (5.2)]*. Consider the use of alternative non-opioid

analgesics in these patients if possible.

5.8 Head Injuries and Increased Intracranial Pressure

Avoid use of DURAGESIC in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma *[see Warnings and Precautions (5.2)]*. In addition, opioids may obscure the clinical course of patients with head injury. Monitor patients with brain tumors who may be susceptible to the intracranial effects of CO_2 retention for signs of sedation and respiratory depression, particularly when initiating therapy with DURAGESIC, as DURAGESIC may reduce respiratory drive and CO_2 retention can further increase intracranial pressure.

5.9 Hypotensive Effects

DURAGESIC may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is an increased risk in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration of certain CNS depressant drugs (e.g., phenothiazines or general anesthetics) *[see Drug Interactions (7.1)]*. Monitor these patients for signs of hypotension after initiating or titrating the dose of DURAGESIC.

5.10 Interactions with CYP3A4 Inhibitors and Inducers

Since the CYP3A4 isoenzyme plays a major role in the metabolism of DURAGESIC, drugs that alter CYP3A4 activity may cause changes in clearance of fentanyl which could lead to changes in fentanyl plasma concentrations.

The concomitant use of DURAGESIC with a CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving DURAGESIC and any CYP3A4 inhibitor for signs of sedation and respiratory depression for an extended period of time, and make dosage adjustments as needed.

CYP450 inducers, such as rifampin, carbamazepine, and phenytoin, may induce the metabolism of fentanyl and, therefore, may cause increased clearance of the drug which could lead to a decrease in fentanyl plasma concentrations, lack of efficacy or, possibly, development of an abstinence syndrome in a patient who had developed physical dependence to fentanyl.

If co-administration is necessary, caution is advised when initiating DURAGESIC treatment in patients currently taking, or discontinuing, CYP3A4 inhibitors or inducers. Evaluate these patients at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Drug Interactions (7.2),* and *Clinical Pharmacology (12.3)]*.

5.11 Application of External Heat

Exposure to heat may increase fentanyl absorption and there have been reports of overdose and death as a result of exposure to heat. A clinical pharmacology study conducted in healthy adult subjects has shown that the application of heat over the DURAGESIC system increased fentanyl exposure *[see Clinical Pharmacology (12.3)]*.

Warn patients to avoid exposing the DURAGESIC application site and surrounding area to direct external heat sources *[see Dosage and Administration (2.3)]*.

5.12 Patients with Fever

Based on a pharmacokinetic model, serum fentanyl concentrations could theoretically increase by approximately one-third for patients with a body temperature of 40°C (104°F) due to temperature-dependent increases in fentanyl released from the system and increased skin permeability. Monitor

patients wearing DURAGESIC systems who develop fever closely for opioid side effects and reduce the DURAGESIC dose if necessary. Warn patients to avoid strenuous exertion that leads to increased core body temperature while wearing DURAGESIC to avoid the risk of potential overdose and death.

5.13 Cardiac Disease

DURAGESIC may produce bradycardia. Monitor patients with bradyarrhythmias closely for changes in heart rate, particularly when initiating therapy with DURAGESIC.

5.14 Hepatic Impairment

A clinical pharmacology study with DURAGESIC in patients with cirrhosis has shown that systemic fentanyl exposure increased in these patients. Because of the long half-life of fentanyl when administered as DURAGESIC and hepatic metabolism of fentanyl, avoid use of DURAGESIC in patients with severe hepatic impairment. Insufficient information exists to make precise dosing recommendations regarding the use of DURAGESIC in patients with impaired hepatic function. Therefore, to avoid starting patients with mild to moderate hepatic impairment on too high of a dose, start with one half of the usual dosage of DURAGESIC. Closely monitor for signs of sedation and respiratory depression, including at each dosage increase. *[see Dosing and Administration (2.2), Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)]*.

5.15 Renal Impairment

A clinical pharmacology study with intravenous fentanyl in patients undergoing kidney transplantation has shown that patients with high blood urea nitrogen level had low fentanyl clearance. Because of the long half-life of fentanyl when administered as DURAGESIC, avoid the use of DURAGESIC in patients with severe renal impairment. Insufficient information exists to make precise dosing recommendations regarding the use of DURAGESIC in patients with impaired renal function. Therefore, to avoid starting patients with mild to moderate renal impairment on too high of a dose, start with one half of the usual dosage of DURAGESIC. Closely monitor for signs of sedation and respiratory depression, including at each dosage increase *[see Dosing and Administration (2.2), Use in Specific Populations (8.7)* and *Clinical Pharmacology (12.3)]*.

5.16 Use in Pancreatic/Biliary Tract Disease

DURAGESIC may cause spasm of the sphincter of Oddi. Monitor patients with biliary tract disease, including acute pancreatitis for worsened symptoms. DURAGESIC may cause increases in the serum amylase concentration.

5.17 Avoidance of Withdrawal

Avoid the use of mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) or partial agonist (buprenorphine) analgesics in patients who have received or are receiving a course of therapy with an opioid agonist analgesic, including DURAGESIC. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

5.18 Driving and Operating Machinery

Strong opioid analgesics impair the mental or physical abilities required for the performance of potentially dangerous tasks, such as driving a car or operating machinery. Warn patients not to drive or operate dangerous machinery unless they are tolerant to the effects of the DURAGESIC.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Addiction, Abuse, and Misuse *[see Warnings and Precautions (5.1)]*

- Life-Threatening Respiratory Depression *[see Warnings and Precautions (5.2)]*
- Accidental Exposure *[see Warnings and Precautions (5.3)]*
- Neonatal Opioid Withdrawal Syndrome *[see Warnings and Precautions (5.4)]*
- Interactions with Central Nervous System Depressants *[see Warnings and Precautions (5.5)]*
- Hypotensive Effects *[see Warnings and Precautions (5.9)]*

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

6.1 Clinical Trial Experience

The safety of DURAGESIC was evaluated in 216 patients who took at least one dose of DURAGESIC in a multicenter, double-blind, randomized, placebo-controlled clinical trial of DURAGESIC. This trial examined patients over 40 years of age with severe pain induced by osteoarthritis of the hip or knee and who were in need of and waiting for joint replacement.

The most common adverse reactions (≥5%) in a double-blind, randomized, placebo-controlled clinical trial in patients with severe pain were nausea, vomiting, somnolence, dizziness, insomnia, constipation, hyperhidrosis, fatigue, feeling cold, and anorexia. Other common adverse reactions (≥5%) reported in clinical trials in patients with chronic malignant or nonmalignant pain were headache and diarrhea. Adverse reactions reported for ≥1% of DURAGESIC-treated patients and with an incidence greater than placebo-treated patients are shown in Table 3.

The most common adverse reactions that were associated with discontinuation in patients with pain (causing discontinuation in ≥1% of patients) were depression, dizziness, somnolence, headache, nausea, vomiting, constipation, hyperhidrosis, and fatigue.

Table 3. Adverse Reactions Reported by ≥1% of DURAGESIC-treated Patients and With an Incidence Greater Than Placebo-treated Patients in 1 Double-Blind, Placebo-Controlled Clinical Trial of DURAGESIC

System/Organ Class Adverse Reaction	DURAGESIC % (N=216)	Placebo % (N=200)
Cardiac disorders		
Palpitations	4	1
Ear and labyrinth disorders		
Vertigo	2	1
Gastrointestinal disorders		
Nausea	41	17
Vomiting	26	3
Constipation	9	1
Abdominal pain upper	3	2
Dry mouth	2	0
General disorders and administration site conditions		
Fatigue	6	3
Feeling cold	6	2
Malaise	4	1
Asthenia	2	0
Edema peripheral	1	1
Metabolism and nutrition disorders		

Anorexia	5	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	4	2
Nervous system disorders		
Somnolence	19	3
Dizziness	10	4
Psychiatric disorders		
Insomnia	10	7
Depression	1	0
Skin and subcutaneous tissue disorders		
Hyperhidrosis	6	1
Pruritus	3	2
Rash	2	1

Adverse reactions not reported in Table 1 that were reported by ≥1% of DURAGESIC-treated adult and pediatric patients (N=1854) in 11 controlled and uncontrolled clinical trials of DURAGESIC used for the treatment of chronic malignant or nonmalignant pain are shown in Table 4.

Table 4. Adverse Reactions Reported by ≥1% of DURAGESIC-treated Patients in 11 Clinical Trials of DURAGESIC

System/Organ Class Adverse Reaction	DURAGESIC % (N=1854)
Gastrointestinal disorders	
Diarrhea	10
Abdominal pain	3
Immune system disorders	
Hypersensitivity	1
Nervous system disorders	
Headache	12
Tremor	3
Paresthesia	2
Psychiatric disorders	
Anxiety	3
Confusional state	2
Hallucination	1
Renal and urinary disorders	
Urinary retention	1
Skin and subcutaneous tissue disorders	
Erythema	1

The following adverse reactions occurred in adult and pediatric patients with an overall frequency of <1% and are listed in descending frequency within each System/Organ Class:

Cardiac disorders: cyanosis
Eye disorders: miosis
Gastrointestinal disorders: subileus

General disorders and administration site conditions: application site reaction, influenza-like illness, application site hypersensitivity, drug withdrawal syndrome, application site dermatitis

Musculoskeletal and connective tissue disorders: muscle twitching

Nervous system disorders: hypoesthesia

Psychiatric disorders: disorientation, euphoric mood

Reproductive system and breast disorders: erectile dysfunction, sexual dysfunction

Respiratory, thoracic and mediastinal disorders: respiratory depression

Skin and subcutaneous tissue disorders: eczema, dermatitis allergic, dermatitis contact

Pediatrics

The safety of DURAGESIC was evaluated in three open-label trials in 289 pediatric patients with chronic pain, 2 years of age through 18 years of age. Adverse reactions reported by ≥1% of DURAGESIC-treated pediatric patients are shown in Table 5.

Table 5. Adverse Reactions Reported by ≥1% of DURAGESIC-treated Pediatric Patients in 3 Clinical Trials of DURAGESIC

System/Organ Class Adverse Reaction	DURAGESIC % (N=289)
Gastrointestinal disorders	
Vomiting	34
Nausea	24
Constipation	13
Diarrhea	13
Abdominal pain	9
Abdominal pain upper	4
Dry mouth	2
General disorders and administration site conditions	
Edema peripheral	5
Fatigue	2
Application site reaction	1
Asthenia	1
Immune system disorders	
Hypersensitivity	3
Metabolism and nutrition disorders	
Anorexia	4
Musculoskeletal and connective tissue disorders	
Muscle spasms	2
Nervous system disorders	
Headache	16
Somnolence	5
Dizziness	2
Tremor	2
Hypoesthesia	1
Psychiatric disorders	
Insomnia	6
Anxiety	4

Depression	2
Hallucination	2
Renal and urinary disorders	
Urinary retention	3
Respiratory, thoracic and mediastinal disorders	
Respiratory depression	1
Skin and subcutaneous tissue disorders	
Pruritus	13
Rash	6
Hyperhidrosis	3
Erythema	3

6.2 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of DURAGESIC. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Cardiac Disorders: tachycardia, bradycardia

Eye Disorders: vision blurred

Gastrointestinal Disorders: ileus, dyspepsia

General Disorders and Administration Site Conditions: pyrexia

Immune System Disorders: anaphylactic shock, anaphylactic reaction, anaphylactoid reaction

Investigations: weight decreased

Nervous System Disorders: convulsions (including clonic convulsions and grand mal convulsion), amnesia, depressed level of consciousness, loss of consciousness

Psychiatric Disorders: agitation

Respiratory, Thoracic, and Mediastinal Disorders: respiratory distress, apnea, bradypnea, hypoventilation, dyspnea

Vascular Disorders: hypotension, hypertension

7 DRUG INTERACTIONS

7.1 Central Nervous System Depressants

The concomitant use of DURAGESIC with other CNS depressants, including sedatives, hypnotics, tranquilizers, general anesthetics, phenothiazines, other opioids, and alcohol, can increase the risk of respiratory depression, profound sedation, coma and death. Monitor patients receiving CNS depressants and DURAGESIC for signs of respiratory depression, sedation and hypotension.

When combined therapy with any of the above medications is considered, the dose of one or both agents should be reduced *[see Dosage and Administration (2.2)* and *Warnings and Precautions (5.5)]*.

7.2 Drugs Affecting Cytochrome P450 3A4 Isoenzymes

Inhibitors of CYP3A4

Because the CYP3A4 isoenzyme plays a major role in the metabolism of fentanyl, drugs that inhibit CYP3A4 activity may cause decreased clearance of fentanyl which could lead to an increase in fentanyl plasma concentrations and result in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of 3A4 inhibitors. If co-administration with DURAGESIC is

necessary, monitor patients for respiratory depression and sedation at frequent intervals and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

Inducers of CYP3A4

CYP450 3A4 inducers may induce the metabolism of fentanyl and, therefore, may cause increased clearance of the drug which could lead to a decrease in fentanyl plasma concentrations, lack of efficacy or, possibly, development of a withdrawal syndrome in a patient who had developed physical dependence to fentanyl. If co-administration with DURAGESIC is necessary, monitor for signs of opioid withdrawal and consider dose adjustments until stable drug effects are achieved *[see Clinical Pharmacology (12.3)]*.

After stopping the treatment of a CYP3A4 inducer, as the effects of the inducer decline, the fentanyl plasma concentration will increase which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression *[see Clinical Pharmacology (12.3)]*.

7.3 MAO Inhibitors

Avoid use of DURAGESIC in the patient who would require the concomitant administration of a monoamine oxidase (MAO) inhibitor, or within 14 days of stopping such treatment because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics.

7.4 Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

Mixed agonist/antagonist (i.e., pentazocine, nalbuphine, and butorphanol) and partial agonist (buprenorphine) analgesics may reduce the analgesic effect of DURAGESIC or may precipitate withdrawal symptoms. Avoid the use of agonist/antagonist and partial agonist analgesics in patients receiving DURAGESIC.

7.5 Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus. Monitor patients for signs of urinary retention or reduced gastrointestinal motility when DURAGESIC is used concurrently with anticholinergic drugs.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Clinical Considerations

Fetal/neonatal adverse reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Observe newborns for symptoms of neonatal opioid withdrawal syndrome, such as poor feeding, diarrhea, irritability, tremor, rigidity, and seizures, and manage accordingly *[see Warnings and Precautions (5.4)]*.

Teratogenic Effects

Pregnancy C: There are no adequate and well-controlled studies in pregnant women. DURAGESIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The potential effects of fentanyl on embryo-fetal development were studied in the rat, mouse, and rabbit models. Published literature reports that administration of fentanyl (0, 10, 100, or 500 µg/kg/day) to pregnant female Sprague-Dawley rats from day 7 to 21 via implanted micro osmotic minipumps did not produce any evidence of teratogenicity (the high dose is approximately 2 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). In contrast, the intravenous administration of

fentanyl (0, 0.01, or 0.03 mg/kg) to bred female rats from gestation day 6 to 18 suggested evidence of embryo-toxicity and a slight increase in mean delivery time in the 0.03 mg/kg/day group. There was no clear evidence of teratogenicity noted.

Pregnant female New Zealand White rabbits were treated with fentanyl (0, 0.025, 0.1, 0.4 mg/kg) via intravenous infusion from day 6 to day 18 of pregnancy. Fentanyl produced a slight decrease in the body weight of the live fetuses at the high dose, which may be attributed to maternal toxicity. Under the conditions of the assay, there was no evidence for fentanyl induced adverse effects on embryo-fetal development at doses up to 0.4 mg/kg (approximately 3 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis).

Nonteratogenic Effects

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures characteristic of neonatal abstinence syndrome in newborn infants. Symptoms of neonatal respiratory or neurological depression were no more frequent than expected in most studies of infants born to women treated acutely during labor with intravenous or epidural fentanyl. Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

The potential effects of fentanyl on prenatal and postnatal development were examined in the rat model. Female Wistar rats were treated with 0, 0.025, 0.1, or 0.4 mg/kg/day fentanyl via intravenous infusion from day 6 of pregnancy through 3 weeks of lactation. Fentanyl treatment (0.4 mg/kg/day) significantly decreased body weight in male and female pups and also decreased survival in pups at day 4. Both the mid-dose and high-dose of fentanyl animals demonstrated alterations in some physical landmarks of development (delayed incisor eruption and eye opening) and transient behavioral development (decreased locomotor activity at day 28 which recovered by day 50). The mid-dose and the high-dose are 0.4 and 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis.

8.2 Labor and Delivery

Opioids cross the placenta and may produce respiratory depression in neonates. DURAGESIC is not for use in women during and immediately prior to labor, when shorter acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, DURAGESIC is not recommended for use in nursing women because of the possibility of effects in their infants.

8.4 Pediatric Use

The safety of DURAGESIC was evaluated in three open-label trials in 289 pediatric patients with chronic pain, 2 years of age through 18 years of age. Starting doses of 25 mcg/h and higher were used by 181 patients who had been on prior daily opioid doses of at least 45 mg/day of oral morphine or an equianalgesic dose of another opioid. Initiation of DURAGESIC therapy in pediatric patients taking less than 60 mg/day of oral morphine or an equianalgesic dose of another opioid has not been evaluated in controlled clinical trials.

The safety and effectiveness of DURAGESIC in children under 2 years of age have not been established.

To guard against excessive exposure to DURAGESIC by young children, advise caregivers to strictly adhere to recommended DURAGESIC application and disposal instructions *[see Dosage and Administration (2.4), (2.5)* and *Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

Clinical studies of DURAGESIC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover, elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the DURAGESIC patch in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours *[see Clinical Pharmacology (12.3)]*.

Monitor geriatric patients closely for signs of sedation and respiratory depression, particularly when initiating therapy with DURAGESIC and when given in conjunction with other drugs that depress respiration *[see Warnings and Precautions (5.2), (5.6)]*.

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of DURAGESIC has not been fully evaluated. A clinical pharmacology study with DURAGESIC in patients with cirrhosis has shown that systemic fentanyl exposure increased in these patients. Because there is in-vitro and in-vivo evidence of extensive hepatic contribution to the elimination of DURAGESIC, hepatic impairment would be expected to have significant effects on the pharmacokinetics of DURAGESIC. Avoid use of DURAGESIC in patients with severe hepatic impairment *[see Dosing and Administration (2.1), Warnings and Precautions (5.14)* and *Clinical Pharmacology 12.3)]*.

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of DURAGESIC has not been fully evaluated. A clinical pharmacology study with intravenous fentanyl in patients undergoing kidney transplantation has shown that patients with high blood urea nitrogen level had low fentanyl clearance. Because there is *in-vivo* evidence of renal contribution to the elimination of DURAGESIC, renal impairment would be expected to have significant effects on the pharmacokinetics of DURAGESIC. Avoid the use of DURAGESIC in patients with severe renal impairment *[see Dosing and Administration (2.1), Warnings and Precautions (5.15)* and *Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

DURAGESIC contains fentanyl, a Schedule II controlled substance with a high potential for abuse similar to other opioids including morphine, hydromorphone, methadone, oxycodone, and oxymorphone. DURAGESIC can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

9.2 Abuse

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even

once, for its rewarding psychological or physiological effects. Drug abuse includes, but is not limited to, the following examples: the use of a prescription or over-the-counter drug to get "high", or the use of steroids for performance enhancement and muscle build up.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and include: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. DURAGESIC, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful recordkeeping of prescribing information, including quantity, frequency, and renewal requests, as required by state law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to the Abuse of DURAGESIC

DURAGESIC is intended for transdermal use only. Abuse of DURAGESIC poses a risk of overdose and death. This risk is increased with concurrent abuse of DURAGESIC with alcohol and other central nervous system depressants *[see Warnings and Precautions (5.5), and Drug Interactions (7.1)]*. Intentional compromise of the transdermal delivery system may result in the uncontrolled delivery of fentanyl and pose a significant risk to the abuser that could result in overdose and death *[see Warnings and Precautions (5.1)]*. Abuse may occur by applying the transdermal system in the absence of legitimate purpose, or by swallowing, snorting or injecting fentanyl extracted from the transdermal system.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dose reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

DURAGESIC should not be abruptly discontinued *[see Dosage and Administration (2.5)]*. If DURAGESIC is abruptly discontinued in a physically-dependent patient, an abstinence syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal symptoms *[see Use in Specific Populations (8.2, 8.3)]*.

10 OVERDOSAGE

10.1 Clinical Presentation

Acute overdosage with opioids can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and sometimes bradycardia, hypotension and death. The pharmacokinetic characteristics of DURAGESIC must also be taken into account when treating the overdose. Even in the face of improvement, continued medical monitoring is required because of the possibility of extended effects. Deaths due to overdose have been reported with abuse and misuse of DURAGESIC.

10.2 Treatment of Overdose

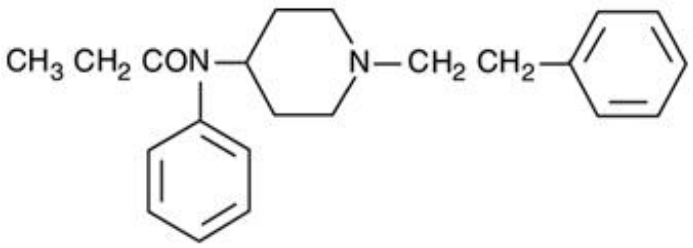
Give primary attention to the reestablishment of a patent airway and institution of assisted or controlled ventilation. Employ supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias will require advanced life support techniques. Remove all DURAGESIC systems.

The pure opioid antagonists, such as naloxone, are specific antidotes to respiratory depression from opioid overdose. Since the duration of reversal is expected to be less than the duration of action of fentanyl, carefully monitor the patient until spontaneous respiration is reliably reestablished. After DURAGESIC system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20–27 hours. Therefore, management of an overdose must be monitored accordingly, at least 72 to 96 hours beyond the overdose.

Only administer opioid antagonists in the presence of clinically significant respiratory or circulatory depression secondary to hydromorphone overdose. In patients who are physically dependent on any opioid agonist including DURAGESIC, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

11 DESCRIPTION

DURAGESIC (fentanyl transdermal system) is a transdermal system containing fentanyl. The chemical name is N-Phenyl-N-(1-(2-phenylethyl)-4-piperidinyl) propanamide. The structural formula is:



The molecular weight of fentanyl base is 336.5, and the empirical formula is $C_{22}H_{28}N_2O$. The n-octanol: water partition coefficient is 860:1. The pKa is 8.4.

System Components and Structure

The amount of fentanyl released from each system per hour is proportional to the surface area (25 mcg/h per 10.5 cm^2). The composition per unit area of all system sizes is identical.

Dose*	Size	Fentanyl Content

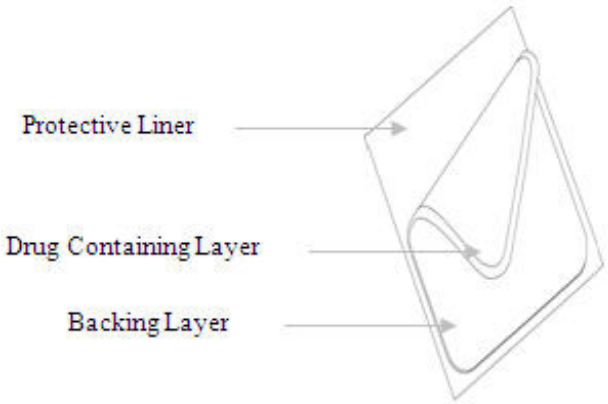
(mcg/h)	(cm^2)	Content (mg)
12†	5.25	2.1
25	10.5	4.2
50	21	8.4
75	31.5	12.6
100	42	16.8

* Nominal delivery rate per hour

† Nominal delivery rate is 12.5 mcg/hr

DURAGESIC is a rectangular transparent unit comprising a protective liner and two functional layers. Proceeding from the outer surface toward the surface adhering to skin, these layers are:

1) a backing layer of polyester/ethyl vinyl acetate film; 2) a drug-in-adhesive layer. Before use, a protective liner covering the adhesive layer is removed and discarded.



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is an opioid analgesic. Fentanyl interacts predominately with the opioid mu-receptor. These mu-binding sites are distributed in the human brain, spinal cord, and other tissues.

12.2 Pharmacodynamics

Central Nervous System Effects

Fentanyl exerts its principal pharmacologic effects on the central nervous system. Central nervous system effects increase with increasing serum fentanyl concentrations.

In addition to analgesia, alterations in mood, euphoria, dysphoria, and drowsiness commonly occur. Fentanyl depresses the respiratory centers, depresses the cough reflex, and constricts the pupils. Analgesic blood concentrations of fentanyl may cause nausea and vomiting directly by stimulating the chemoreceptor trigger zone, but nausea and vomiting are significantly more common in ambulatory than in recumbent patients, as is postural syncope.

Ventilatory Effects

In clinical trials of 357 non-opioid tolerant subjects treated with DURAGESIC, 13 subjects experienced hypoventilation. Hypoventilation was manifested by respiratory rates of less than 8 breaths/minute or a pCO_2 greater than 55 mm Hg. In these studies, the incidence of hypoventilation was higher in nontolerant women (10) than in men (3) and in subjects weighing less than 63 kg (9 of 13). Although

subjects with prior impaired respiration were not common in the trials, they had higher rates of hypoventilation. In addition, post-marketing reports have been received that describe opioid-naive post-operative patients who have experienced clinically significant hypoventilation and death with DURAGESIC.

Hypoventilation can occur throughout the therapeutic range of fentanyl serum concentrations, especially for patients who have an underlying pulmonary condition or who receive concomitant opioids or other CNS drugs associated with hypoventilation. The use of DURAGESIC is contraindicated in patients who are not tolerant to opioid therapy.

Gastrointestinal Tract and Other Smooth Muscle

Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Because opioids may increase biliary tract pressure, some patients with biliary colic may experience worsening rather than relief of pain.

While opioids generally increase the tone of urinary tract smooth muscle, the net effect tends to be variable, in some cases producing urinary urgency, in others, difficulty in urination.

Cardiovascular Effects

Fentanyl may cause orthostatic hypotension and fainting. Fentanyl may infrequently produce bradycardia. The incidence of bradycardia in clinical trials with DURAGESIC was less than 1%.

Histamine assays and skin wheal testing in clinical studies indicate that clinically significant histamine release rarely occurs with fentanyl administration. Clinical assays show no clinically significant histamine release in dosages up to 50 mcg/kg.

12.3 Pharmacokinetics

Absorption

DURAGESIC is a drug-in-adhesive matrix designed formulation. Fentanyl is released from the matrix at a nearly constant amount per unit time. The concentration gradient existing between the matrix and the lower concentration in the skin drives drug release. Fentanyl moves in the direction of the lower concentration at a rate determined by the matrix and the diffusion of fentanyl through the skin layers. While the actual rate of fentanyl delivery to the skin varies over the 72-hour application period, each system is labeled with a nominal flux which represents the average amount of drug delivered to the systemic circulation per hour across average skin.

While there is variation in dose delivered among patients, the nominal flux of the systems (12.5, 25, 50, 75, and 100 mcg of fentanyl per hour) is sufficiently accurate as to allow individual titration of dosage for a given patient.

Following DURAGESIC application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. Serum fentanyl concentrations increase gradually following initial DURAGESIC application, generally leveling off between 12 and 24 hours and remaining relatively constant, with some fluctuation, for the remainder of the 72-hour application period. Peak serum concentrations of fentanyl generally occurred between 20 and 72 hours after initial application (see Table 6). Serum fentanyl concentrations achieved are proportional to the DURAGESIC delivery rate. With continuous use, serum fentanyl concentrations continue to rise for the first two system applications. By the end of the second 72-hour application, a steady-state serum concentration is reached and is maintained during subsequent applications of a patch of the same size (see Figure 1). Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl.

After system removal, serum fentanyl concentrations decline gradually, falling about 50% in approximately 20–27 hours. Continued absorption of fentanyl from the skin accounts for a slower disappearance of the drug from the serum than is seen after an IV infusion, where the apparent half-life

is approximately 7 (range 3–12) hours.

A clinical pharmacology study conducted in healthy adult subjects has shown that the application of heat over the DURAGESIC system increased mean overall fentanyl exposure by 120% and average maximum fentanyl level by 61%.

Table 6: FENTANYL PHARMACOKINETIC PARAMETERS FOLLOWING FIRST 72-HOUR APPLICATION OF DURAGESIC

	Mean (SD) Time to Maximal Concentration T_{max} (h)	Mean (SD) Maximal Concentration C_{max} (ng/mL)
DURAGESIC 12 mcg/h	28.8 (13.7)	0.38 (0.13)*
DURAGESIC 25 mcg/h	31.7 (16.5)	0.85 (0.26)†
DURAGESIC 50 mcg/h	32.8 (15.6)	1.72 (0.53)†
DURAGESIC 75 mcg/h	35.8 (14.1)	2.32 (0.86)†
DURAGESIC 100 mcg/h	29.9 (13.3)	3.36 (1.28)†

NOTE: After system removal there is continued systemic absorption from residual fentanyl in the skin so that serum concentrations fall 50%, on average, in approximately 20–27 hours.

* C_{max} values dose normalized from 4 × 12.5 mcg/h: Study 2003-038 in healthy volunteers

† C_{max} values: Study C-2002-048 dose proportionality study in healthy volunteers

Figure 1 Serum Fentanyl Concentrations Following Single and Multiple Applications of DURAGESIC 100 mcg/h

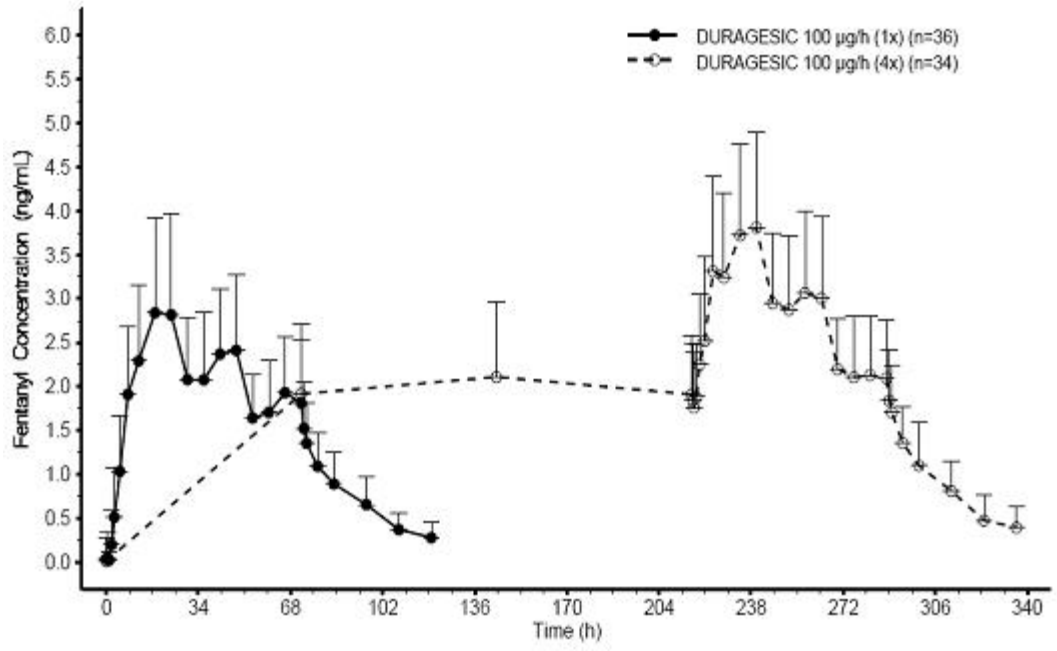


Table 7: RANGE OF PHARMACOKINETIC PARAMETERS OF INTRAVENOUS FENTANYL IN PATIENTS

	Clearance (L/h) Range	Volume of Distribution V_{SS} (L/kg)	Half-Life $t_{1/2}$ (h)

	[70 kg]	(L/kg) Range	Range
Surgical Patients	27–75	3–8	3–12
Hepatically Impaired Patients	3–80*	0.8–8*	4–12*
Renally Impaired Patients	30–78	–	–

NOTE: Information on volume of distribution and half-life not available for renally impaired patients.

* Estimated

Distribution

Fentanyl plasma protein binding capacity decreases with increasing ionization of the drug. Alterations in pH may affect its distribution between plasma and the central nervous system. Fentanyl accumulates in the skeletal muscle and fat and is released slowly into the blood. The average volume of distribution for fentanyl is 6 L/kg (range 3–8; N=8).

Metabolism

Fentanyl is metabolized primarily via human cytochrome P450 3A4 isoenzyme system. In humans, the drug appears to be metabolized primarily by oxidative N-dealkylation to norfentanyl and other inactive metabolites that do not contribute materially to the observed activity of the drug.

Excretion

Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted in urine, mostly as metabolites with less than 10% representing unchanged drug. Approximately 9% of the dose is recovered in the feces, primarily as metabolites. Mean values for unbound fractions of fentanyl in plasma are estimated to be between 13 and 21%.

Skin does not appear to metabolize fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Specific Populations

Geriatric Use

Data from intravenous studies with fentanyl suggest that the elderly patients may have reduced clearance and a prolonged half-life. Moreover elderly patients may be more sensitive to the active substance than younger patients. A study conducted with the DURAGESIC fentanyl transdermal patch in elderly patients demonstrated that fentanyl pharmacokinetics did not differ significantly from young adult subjects, although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. In this study, a single DURAGESIC 100 µg/hour patch was applied to a skin site on the upper outer arm in a group of healthy elderly Caucasians ≥65 years old (n=21, mean age 71 years) and worn for 72 hours. The mean C_{max} and AUC_{∞} values were approximately 8% lower and 7% higher, respectively, in the elderly subjects as compared with subjects 18 to 45 years old. Inter-subject variability in AUC∞ was higher in elderly subjects than in healthy adult subjects 18 to 45 years (58% and 37%, respectively). The mean half-life value was longer in subjects ≥65 years old than in subjects 18 to 45 years old (34.4 hours versus 23.5 hours) *[see Warnings and Precautions (5.6)* and *Use in Specific Populations (8.5)]*.

Pediatric Use

In 1.5 to 5 year old, non-opioid-tolerant pediatric patients, the fentanyl plasma concentrations were approximately twice as high as that of adult patients. In older pediatric patients, the pharmacokinetic parameters were similar to that of adults. However, these findings have been taken into consideration in determining the dosing recommendations for opioid-tolerant pediatric patients (2 years of age and

older). For pediatric dosing information, refer to *[see Dosing and Administration (2.1)]*.

Hepatic Impairment

Information on the effect of hepatic impairment on the pharmacokinetics of DURAGESIC is limited. The pharmacokinetics of DURAGESIC delivering 50 µg/hour of fentanyl for 72 hours was evaluated in patients hospitalized for surgery. Compared to the controlled patients (n=8), C_{max} and AUC in the patients with cirrhosis (n=9) increased 35% and 73%, respectively.

Because there is *in-vitro* and *in-vivo* evidence of extensive hepatic contribution to the elimination of DURAGESIC, hepatic impairment would be expected to have significant effects on the pharmacokinetics of DURAGESIC. Avoid use of DURAGESIC in patients with severe hepatic impairment *[see Dosing and Administration (2.1), Warnings and Precautions (5.14),* and *Use in Specific Populations (8.6)]*.

Renal Impairment

Information on the effect of renal impairment on the pharmacokinetics of DURAGESIC is limited. The pharmacokinetics of intravenous injection of 25 µg/kg fentanyl was evaluated in patients (n=8) undergoing kidney transplantation. An inverse relationship between blood urea nitrogen level and fentanyl clearance was found.

Because there is *in-vivo* evidence of renal contribution to the elimination of DURAGESIC, renal impairment would be expected to have significant effects on the pharmacokinetics of DURAGESIC. Avoid the use of DURAGESIC in patients with severe renal impairment *[see Dosing and Administration (2.1), Warnings and Precautions (5.15)* and *Use in Specific Populations (8.7)]*.

Drug-Drug Interactions

CYP3A4 Inhibitors

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4). The interaction between ritonavir, a CPY3A4 inhibitor, and fentanyl was investigated in eleven healthy volunteers in a randomized crossover study. Subjects received oral ritonavir or placebo for 3 days. The ritonavir dose was 200 mg tid on Day 1 and 300 mg tid on Day 2 followed by one morning dose of 300 mg on Day 3. On Day 2, fentanyl was given as a single IV dose at 5 mcg/kg two hours after the afternoon dose of oral ritonavir or placebo. Naloxone was administered to counteract the side effects of fentanyl. The results suggested that ritonavir might decrease the clearance of fentanyl by 67%, resulting in a 174% (range 52%–420%) increase in fentanyl $AUC_{0-\infty}$. The concomitant use of transdermal fentanyl with all CYP3A4 inhibitors (such as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, nelfinavir, nefazadone, amiodarone, amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil, or grapefruit juice) may result in an increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Carefully monitor patients receiving DURAGESIC and any CYP3A4 inhibitor for signs of respiratory depression for an extended period of time and adjust the dosage if warranted *[see Boxed Warning* and *Warnings and Precautions (5.10), and Drug Interactions (7.2)]*.

CYP3A4 Inducers

Co-administration with agents that induce CYP3A4 activity may reduce the efficacy of DURAGESIC.

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a two-year carcinogenicity study conducted in rats, fentanyl was not associated with an increased incidence of tumors at subcutaneous doses up to 33 µg/kg/day in males or 100 µg/kg/day in females

(0.16 and 0.39 times the human daily exposure obtained via the 100 mcg/h patch based on AUC_{0-24h} comparison).

Mutagenesis

There was no evidence of mutagenicity in the Ames Salmonella mutagenicity assay, the primary rat hepatocyte unscheduled DNA synthesis assay, the BALB/c 3T3 transformation test, and the human lymphocyte and CHO chromosomal aberration *in-vitro* assays.

Impairment of Fertility

The potential effects of fentanyl on male and female fertility were examined in the rat model via two separate experiments. In the male fertility study, male rats were treated with fentanyl (0, 0.025, 0.1 or 0.4 mg/kg/day) via continuous intravenous infusion for 28 days prior to mating; female rats were not treated. In the female fertility study, female rats were treated with fentanyl (0, 0.025, 0.1 or 0.4 mg/kg/day) via continuous intravenous infusion for 14 days prior to mating until day 16 of pregnancy; male rats were not treated. Analysis of fertility parameters in both studies indicated that an intravenous dose of fentanyl up to 0.4 mg/kg/day to either the male or the female alone produced no effects on fertility (this dose is approximately 1.6 times the daily human dose administered by a 100 mcg/hr patch on a mg/m^2 basis). In a separate study, a single daily bolus dose of fentanyl was shown to impair fertility in rats when given in intravenous doses of 0.3 times the human dose for a period of 12 days.

14 CLINICAL STUDIES

DURAGESIC as therapy for pain due to cancer has been studied in 153 patients. In this patient population, DURAGESIC has been administered in doses of 25 µg/h to 600 µg/h. Individual patients have used DURAGESIC continuously for up to 866 days. At one month after initiation of DURAGESIC therapy, patients generally reported lower pain intensity scores as compared to a prestudy analgesic regimen of oral morphine.

The duration of DURAGESIC use varied in cancer patients; 56% of patients used DURAGESIC for over 30 days, 28% continued treatment for more than 4 months, and 10% used DURAGESIC for more than 1 year.

In the pediatric population, the safety of DURAGESIC has been evaluated in 289 patients with chronic pain 2–18 years of age. The duration of DURAGESIC use varied; 20% of pediatric patients were treated for ≤ 15 days; 46% for 16–30 days; 16% for 31–60 days; and 17% for at least 61 days. Twenty-five patients were treated with DURAGESIC for at least 4 months and 9 patients for more than 9 months.

16 HOW SUPPLIED/STORAGE AND HANDLING

DURAGESIC (fentanyl transdermal system) is supplied in cartons containing 5 individually packaged systems. See chart for information regarding individual systems.

DURAGESIC Dose (mcg/h)	System Size (cm^2)	Fentanyl Content (mg)	NDC Number
DURAGESIC-12*	5.25	2.1	50458-090-05
DURAGESIC-25	10.5	4.2	50458-091-05
DURAGESIC-50	21	8.4	50458-092-05
DURAGESIC-75	31.5	12.6	50458-093-05
DURAGESIC-100	42	16.8	50458-094-05

* This lowest dosage is designated as 12 mcg/h (however, the actual dosage is 12.5 mcg/h) to distinguish it from a 125 mcg/h dosage that could be prescribed by using multiple patches.

Store in original unopened pouch. Store up to 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Addiction, Abuse, and Misuse

Inform patients that the use of DURAGESIC, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose or death *[see Warnings and Precautions (5.1)]*. Instruct patients not to share DURAGESIC with others and to take steps to protect DURAGESIC from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting DURAGESIC or when the dose is increased, and that it can occur even at recommended doses *[see Warnings and Precautions (5.2)]*. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

Accidental Exposure

Inform patients to keep DURAGESIC in a secure place out of the reach of children due to the high risk of respiratory depression or death. *[see Warnings and Precautions (5.3)]*. DURAGESIC can be accidentally transferred to children. Instruct patients to take special precautions to avoid accidental contact when holding or caring for children.

Instruct patients that, if the patch dislodges and accidentally sticks to the skin of another person, to immediately take the patch off, wash the exposed area with water and seek medical attention for the accidentally exposed individual as accidental exposure may lead to death or other serious medical problems.

Neonatal Opioid Withdrawal Syndrome

Inform female patients of reproductive potential that prolonged use of DURAGESIC during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated *[see Warnings and Precautions (5.4)]*.

Interactions with Alcohol and other CNS Depressants

Inform patients that potentially serious additive effects may occur if DURAGESIC is used with alcohol or other CNS depressants, and not to use such drugs unless supervised by a healthcare provider.

Important Administration Instructions

Advise patients never to change the dose of DURAGESIC or the number of patches applied to the skin unless instructed to do so by the prescribing healthcare professional.

When no longer needed, advise patients how to safely taper DURAGESIC and not to stop it abruptly to avoid the risk of precipitating withdrawal symptoms.

Warnings About Heat

Warn patients of the potential for temperature-dependent increases in fentanyl release from the patch that could result in an overdose of fentanyl. Instruct patients to contact their healthcare provider if they develop a high fever. Instruct patients to:

- avoid strenuous exertion that can increase body temperature while wearing the patch
- avoid exposing the DURAGESIC application site and surrounding area to direct external heat sources including heating pads, electric blankets, sunbathing, heat or tanning lamps, saunas, hot tubs or hot baths, and heated water beds.

Driving or Operating Heavy Machinery

DURAGESIC may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Instruct patients to refrain from any potentially dangerous activity when starting on DURAGESIC or when their dose is being adjusted, until it is established that they have not been adversely affected.

Pregnancy

Advise women of childbearing potential who become, or are planning to become pregnant, to consult a healthcare provider prior to initiating or continuing therapy with DURAGESIC.

Additive Effects of Alcohol and other CNS Depressants

Instruct patients not to use alcohol or other CNS depressants (e.g. sleep medications, tranquilizers) while using DURAGESIC because dangerous additive effects may occur, resulting in serious injury or death.

Constipation

Advise patients of the potential for severe constipation.

Disposal

Instruct patients to refer to the Instructions for Use for proper disposal of DURAGESIC. To properly dispose of a used patch, instruct patients to remove it, fold so that the adhesive side of the patch adheres to itself, and immediately flush down the toilet. Unused patches should be removed from their pouches, the protective liners removed, the patches folded so that the adhesive side of the patch adheres to itself, and immediately flushed down the toilet.

Instruct patients to dispose of any patches remaining from a prescription as soon as they are no longer needed.

Manufactured by:
ALZA Corporation
Vacaville, CA 95688

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Revised April 2014

Medication Guide
DURAGESIC® (Dur-ah-GEE-zik) (fentanyl) Transdermal System, CII

DURAGESIC® is:

- A strong prescription pain medicine that contains an opioid (narcotic) that is used to manage pain severe enough to require daily around-the-clock, long-term treatment with an opioid, in people who are already regularly using opioid pain medicine, when other pain treatments such as non-opioid pain medicines or immediate-release opioid medicines do not treat your pain well enough or you cannot tolerate them.
- A long-acting (extended-release) opioid pain medicine that can put you at risk for overdose and death. Even if you take your dose correctly as prescribed you are at risk for opioid addiction, abuse, and misuse that can lead to death.
- Not for use to treat pain that is not around-the-clock.

Important information about DURAGESIC®:

- **Get emergency help right away if you use too much DURAGESIC® (overdose).** When you first

start taking DURAGESIC®, when your dose is changed, or if you take too much (overdose), serious or life threatening breathing problems that can lead to death may occur.
- Never give anyone else your DURAGESIC®. They could die from using it. Store DURAGESIC® away from children and in a safe place to prevent stealing or abuse. Selling or giving away DURAGESIC® is against the law.
- If the patch accidentally sticks to a family member while in close contact, take the patch off, wash the area with water, and get emergency help right away because an accidental exposure to DURAGESIC® can lead to death or other serious medical problems.
- Proper disposal of DURAGESIC® after use and for unused patches when no longer needed: Fold the sticky sides of the patch together and flush down the toilet. Do not put patches in a trash can.

Do not use DURAGESIC® if you have:
- severe asthma, trouble breathing, or other lung problems.
- a bowel blockage or have narrowing of the stomach or intestines.

Before applying DURAGESIC®, tell your healthcare provider if you have a history of:
- head injury, seizures
- problems urinating
- abuse of street or prescription drugs, alcohol addiction, or mental health problems.
- liver, kidney, thyroid problems
- pancreas or gallbladder problems

Tell your healthcare provider if you:
- have a fever
- **are pregnant or planning to become pregnant.** Prolonged use of DURAGESIC® during pregnancy can cause withdrawal symptoms in your newborn baby that could be life-threatening if not recognized and treated.
- **are breastfeeding.** DURAGESIC® passes into breast milk and may harm your baby.
- are taking prescription or over-the-counter medicines, vitamins, or herbal supplements. Taking DURAGESIC® with certain other medicines can cause serious side effects that could lead to death.

When using DURAGESIC®:
- Do not change your dose. Apply DURAGESIC® exactly as prescribed by your healthcare provider.
- See the detailed Instructions for Use for information about how to apply and dispose of the DURAGESIC® patch.
- Do not apply more than 1 patch at the same time unless your healthcare provider tells you to.
- You should wear the DURAGESIC® patch continuously for 3 days, unless advised otherwise by your healthcare provider.
- **Call your healthcare provider if the dose you are using does not control your pain.**
- **Do not stop using DURAGESIC® without talking to your healthcare provider.**

While using DURAGESIC® DO NOT:
- Take hot baths or sunbathe, use hot tubs, saunas, heating pads, electric blankets, heated waterbeds, or tanning lamps, or engage in exercise that increases your body temperature. These can cause an overdose that can lead to death.
- Drive or operate heavy machinery, until you know how DURAGESIC® affects you. DURAGESIC® can make you sleepy, dizzy, or lightheaded.
- Drink alcohol or use prescription or over-the-counter medicines that contain alcohol. Using products containing alcohol during treatment with DURAGESIC® may cause you to overdose and die.

The possible side effects of DURAGESIC® are:
- constipation, nausea, sleepiness, vomiting, tiredness, headache, dizziness, abdominal pain, itching,

redness, or rash where the patch is applied. Call your healthcare provider if you have any of these symptoms and they are severe.

Get emergency medical help if you have:

- trouble breathing, shortness of breath, fast heartbeat, chest pain, swelling of your face, tongue or throat, extreme drowsiness, light-headedness when changing positions, or you are feeling faint.

These are not all the possible side effects of DURAGESIC®. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. **For more information go to dailymed.nlm.nih.gov**

Manufactured by: Alza Corporation, Vacaville, CA 95688; Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560, www.Duragesic.com or call 1-800-526-7736

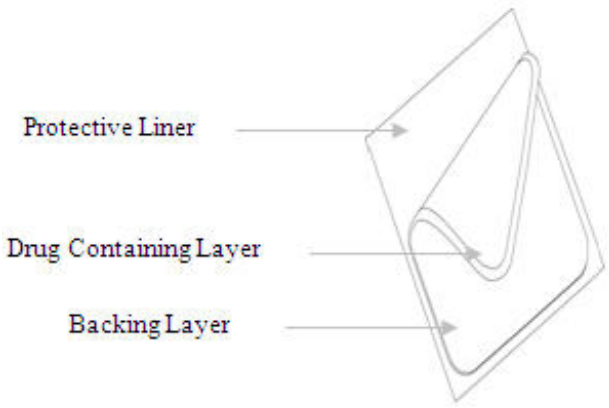
This Medication Guide has been approved by the U.S. Food and Drug Administration.
Revised: April 2014

Instructions for Use
DURAGESIC® (Dur-ah-GEE-zik)
(Fentanyl Transdermal System) CII

Instructions for Applying a DURAGESIC® patch

Be sure that you read, understand, and follow these Instructions for Use before you use DURAGESIC®. Talk to your healthcare provider or pharmacist if you have any questions.

Parts of the DURAGESIC® patch:



Before applying DURAGESIC®

- **Each DURAGESIC® patch is sealed in its own protective pouch. Do not remove a DURAGESIC® patch from the pouch until you are ready to use it.**
- **Do not use a DURAGESIC® patch if the pouch seal is broken or the patch is cut, damaged or changed in any way.**
- **DURAGESIC® patches are available in 5 different doses and patch sizes. Make sure you have the right dose patch or patches that have been prescribed for you.**

<u>Applying a DURAGESIC® patch</u>

1. **<u>Skin areas where the DURAGESIC® patch may be applied:</u>**

For adults:

- Put the patch on the chest, back, flank (sides of the waist), or upper arm in a place where there is no hair (See Figures A–D).

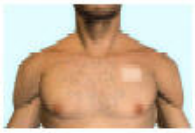


Figure A

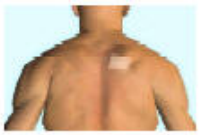


Figure B

For children (and adults with mental impairment):

- **Put the patch on the upper back (See Figure B).** This will lower the chances that the child will remove the patch and put it in their mouth.

Figure C

For adults and children

- <u>Do not</u> put a DURAGESIC® patch on skin that is very oily, burned, broken out, cut, irritated, or damaged in any way.
- Avoid sensitive areas or those that move around a lot. If there is hair, **do not shave (shaving irritates the skin)**. Instead, clip hair as close to the skin as possible (See Figure E).
- **Talk to your healthcare provider if you have questions about skin application sites.**

Figure D

Figure E

2. **Prepare to apply a DURAGESIC® patch:**

- Choose the time of day that is best for you to apply DURAGESIC®. Change it at about the same time of day (3 days or 72 hours after you apply the patch) or as directed by your healthcare provider.
- Do not wear more than one DURAGESIC® patch at a time unless your healthcare provider tells you to do so. Before applying a new DURAGESIC® patch, remove the patch you have been wearing.
- Clean the skin area with clear water **only**. **Pat skin completely dry.** Do not use anything on the skin such as soaps, lotions, oils, or alcohol before the patch is applied.

3. **Open the pouch:** Fold and tear at slit, or cut at slit taking care not to cut the patch. Remove the DURAGESIC® patch. Each DURAGESIC® patch is sealed in its own protective pouch. Do not remove the DURAGESIC® patch from the pouch until you are ready to use it (See Figure F).

Figure F

4. **Peel:** Peel off both parts of the protective liner from the

patch. Each DURAGESIC® patch has a clear plastic backing that can be peeled off in two pieces. This covers the sticky side of the patch. Carefully peel this backing off. Throw the clear plastic backing away. **Touch the sticky side of the DURAGESIC® patch as little as possible** (See Figure G).

Figure G

5. **Press:** Press the patch onto the chosen skin site **with the palm of your hand and hold there for at least 30 seconds** (See Figure H). Make sure it sticks well, especially at the edges.
   - DURAGESIC® may not stick to all patients. You need to check the patches often to make sure that they are sticking well to the skin.
   - If the patch falls off right away after applying, throw it away and put a new one on at a different skin site. See the section below called "Disposing of a DURAGESIC® patch".
   - If you have a problem with the patch not sticking
     - Apply first aid tape only to the edges of the patch.
     - If you continue to have problems with the patch sticking, you may cover the patch with Bioclusive™ or Tegaderm™. These are special see-through adhesive dressings. **Never cover a DURAGESIC® patch with any other bandage or tape.** Remove the backing from the Bioclusive™ or Tegaderm™ dressing and place it carefully over the DURAGESIC® patch, smoothing it over the patch and your skin.
   - **If your patch falls off later, but before 3 days (72 hours) of use, dispose of properly. See the section below "Disposing of a DURAGESIC® patch". Apply a new DURAGESIC® patch on at a different skin site. Be sure to let your healthcare provider know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your healthcare provider).**

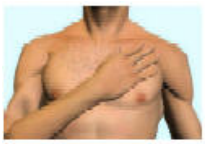


Figure H

6. Wash your hands when you have finished applying a DURAGESIC® patch.

7. Remove a DURAGESIC® patch after wearing it for 3 days (72 hours). See the section below "Disposing of a DURAGESIC® patch". Choose a **different** skin site to apply a new DURAGESIC® patch. Repeat Steps 2 through 6 above when applying a new DURAGESIC® patch.

Do not apply the new patch to the same place as the last one.

Water and DURAGESIC®

- You can bathe, swim or shower while you are wearing a DURAGESIC® patch. If the patch falls off before 3 days (72 hours) after application, dispose of properly. See the section below "Disposing of a DURAGESIC® patch". Apply a new DURAGESIC® patch on at a different skin site. Be sure to let your healthcare provider know that this has happened, and do not replace the new patch until 3 days (72 hours) after you put it on (or as directed by your healthcare provider).

Disposing of a DURAGESIC® patch

- Fold the used DURAGESIC® patch in half so that the sticky side sticks to itself (See Figure I). **Flush the used DURAGESIC® patch down the toilet right away** (See Figure J). **A used DURAGESIC® patch can be very dangerous for or lead to death in babies, children, pets, and adults who have not been prescribed DURAGESIC®.**
- Throw away any DURAGESIC® patches that are left over from your prescription as soon as they are no longer needed. Remove the leftover patches from their protective pouch and remove the protective liner. **Fold the patches in half with the sticky sides together, and flush the patches down the toilet.** Do not flush the pouch or the protective liner down the toilet. These items can be thrown away in a trashcan.

Figure I

Figure J

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Manufactured by:
ALZA Corporation
Vacaville, CA 95688

Manufactured for:
Janssen Pharmaceuticals, Inc.
Titusville, NJ 08560

Revised: April 2014

Bioclusive™ is a trademark of Ethicon, Inc.
Tegaderm™ is a trademark of 3M

PRINCIPAL DISPLAY PANEL - 12 mcg/h Patch Carton

NDC 50458-090-05
Five (12mcg/h) **Systems**

DURAGESIC® 12 mcg/h
(FENTANYL TRANSDERMAL SYSTEM)

CII

In vivo delivery of 12mcg/h fentanyl for 72 hours

Because serious or life-threatening breathing problems could result, DO NOT USE DURAGESIC:

- for pain that can be treated with immediate-release opioids or non-opioid analgesics
- for intermittent (on an as-needed basis) pain
- for any postoperative pain
- unless you are opioid tolerant (have been using other narcotic opioid medicines)

Each transdermal system contains: 2.1mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

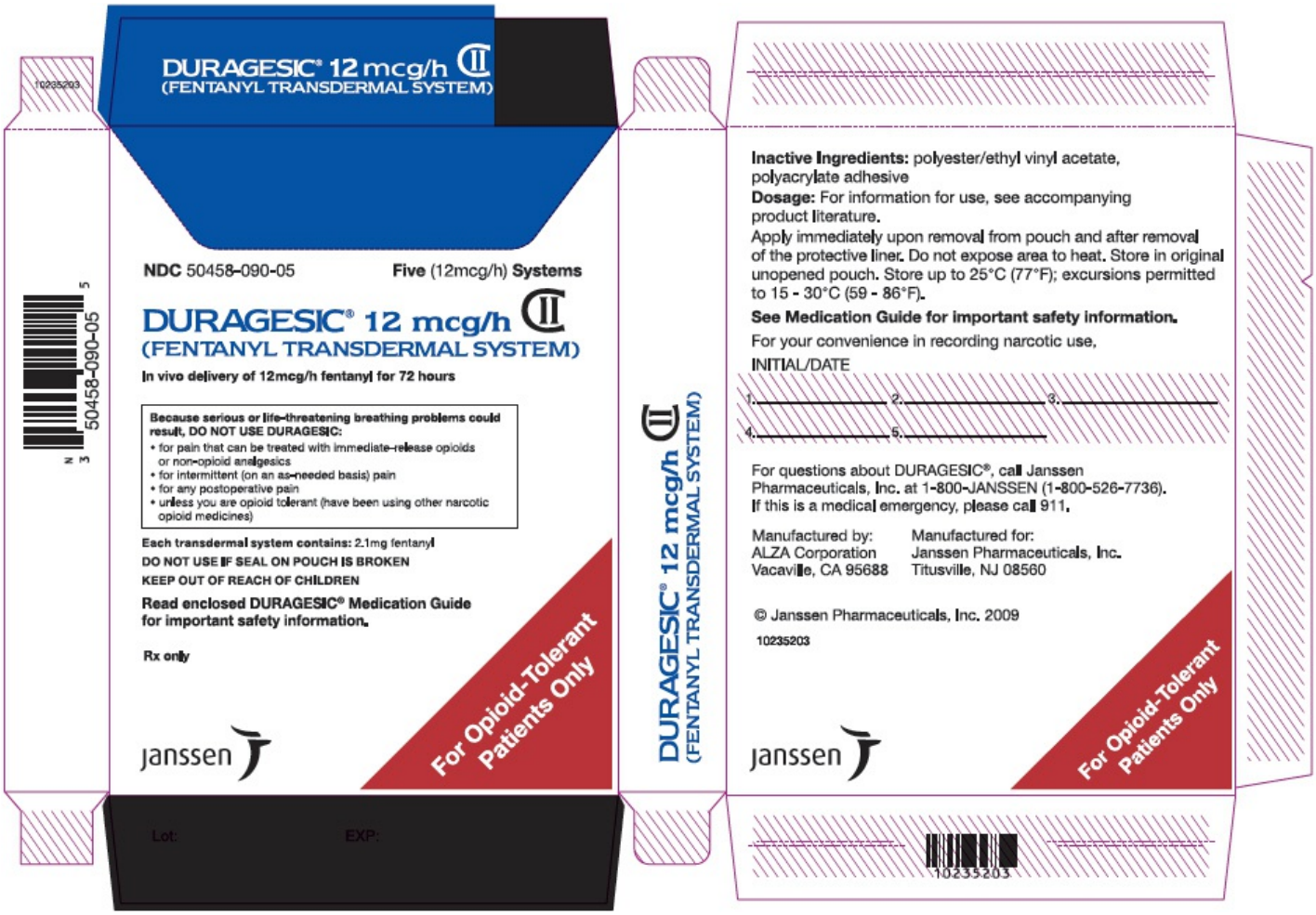
KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

For Opioid-Tolerant Patients Only

Janssen



PRINCIPAL DISPLAY PANEL - 25 mcg/h Patch Carton

NDC 50458-091-05
Five (25mcg/h) **Systems**

DURAGESIC® 25 mcg/h
(FENTANYL TRANSDERMAL SYSTEM)
CII

In vivo delivery of 25mcg/h fentanyl for 72 hours

Because serious or life-threatening breathing problems could result, DO NOT USE DURAGESIC:

- for pain that can be treated with immediate-release opioids or non-opioid analgesics
- for intermittent (on an as-needed basis) pain
- for any postoperative pain
- unless you are opioid tolerant (have been using other narcotic opioid medicines)

Each transdermal system contains: 4.2mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

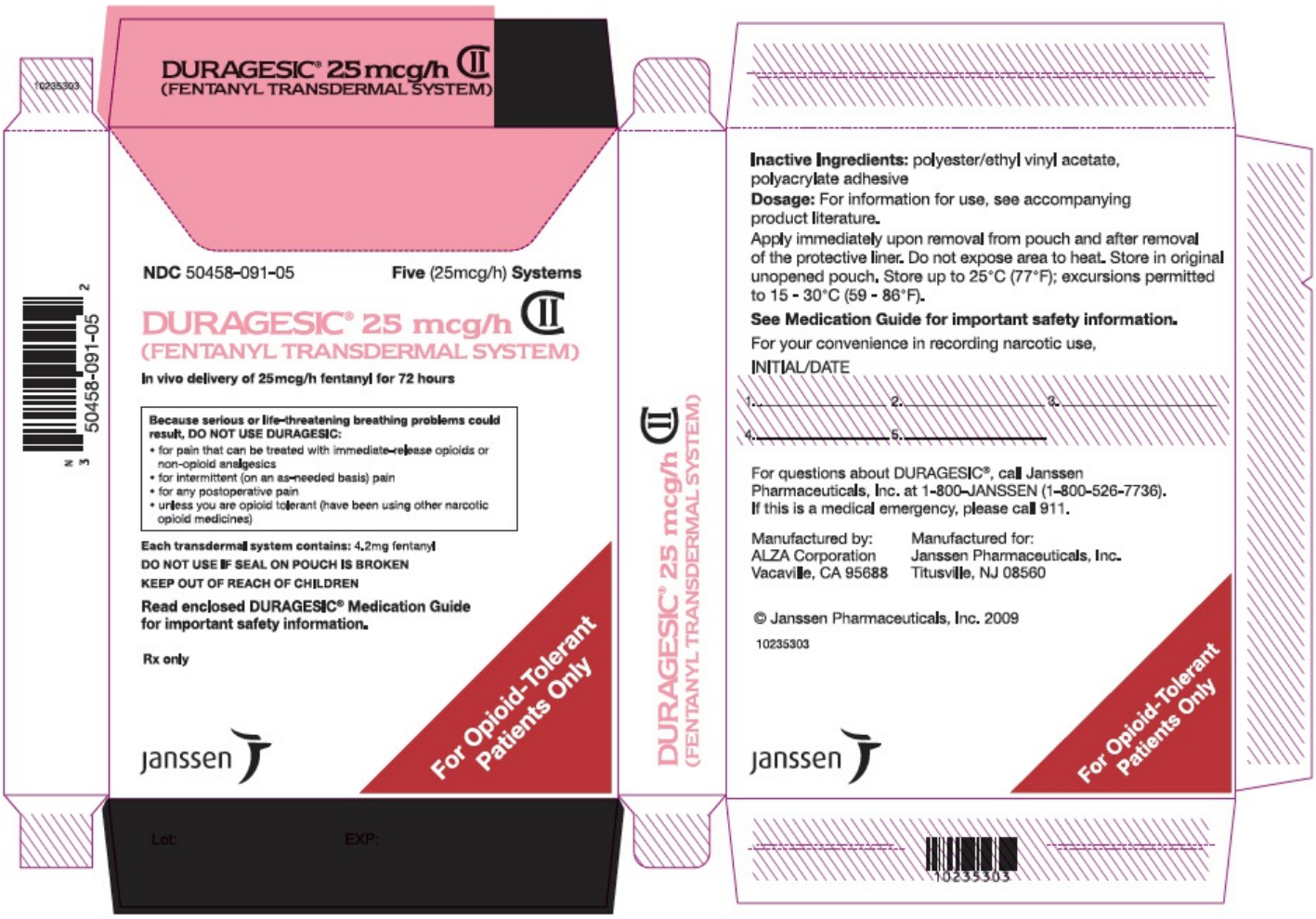
KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

For Opioid-Tolerant Patients Only

Janssen



PRINCIPAL DISPLAY PANEL - 50 mcg/h Patch Carton

NDC 50458-092-05
Five (50mcg/h) **Systems**

DURAGESIC® 50 mcg/h
(FENTANYL TRANSDERMAL SYSTEM)
CII

In vivo delivery of 50mcg/h fentanyl for 72 hours

Because serious or life-threatening breathing problems could result, DO NOT USE DURAGESIC:

- for pain that can be treated with immediate-release opioids or non-opioid analgesics
- for intermittent (on an as-needed basis) pain
- for any postoperative pain
- unless you are opioid tolerant (have been using other narcotic opioid medicines)

Each transdermal system contains: 8.4mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

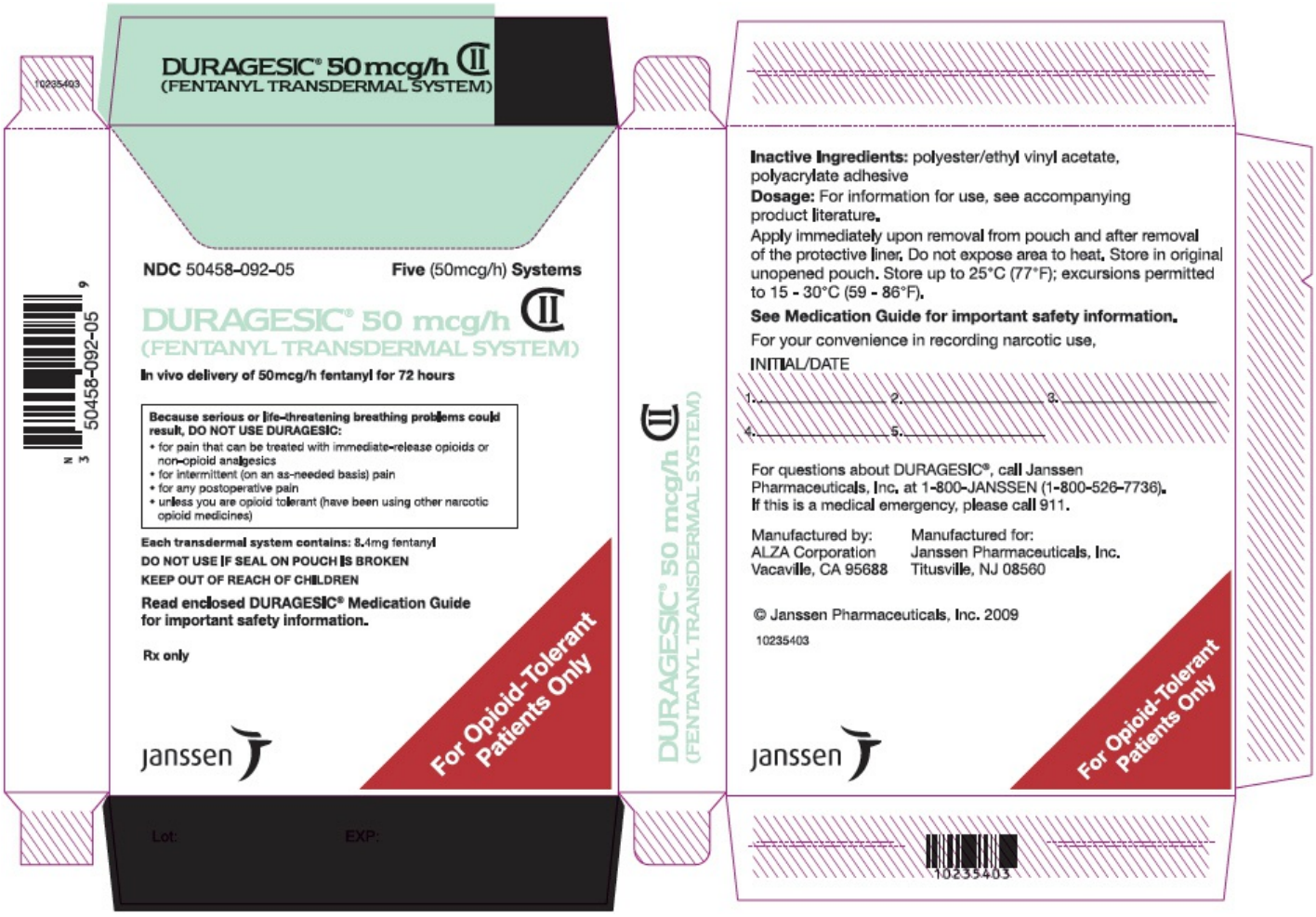
KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

For Opioid-Tolerant Patients Only

Janssen



PRINCIPAL DISPLAY PANEL - 75 mcg/h Patch Carton

NDC 50458-093-05
Five (75mcg/h) **Systems**

DURAGESIC® 75 mcg/h
(FENTANYL TRANSDERMAL SYSTEM)
CII

In vivo delivery of 75mcg/h fentanyl for 72 hours

Because serious or life-threatening breathing problems could result, DO NOT USE DURAGESIC:

- for pain that can be treated with immediate-release opioids or non-opioid analgesics
- for intermittent (on an as-needed basis) pain
- for any postoperative pain
- unless you are opioid tolerant (have been using other narcotic opioid medicines)

Each transdermal system contains: 12.6mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

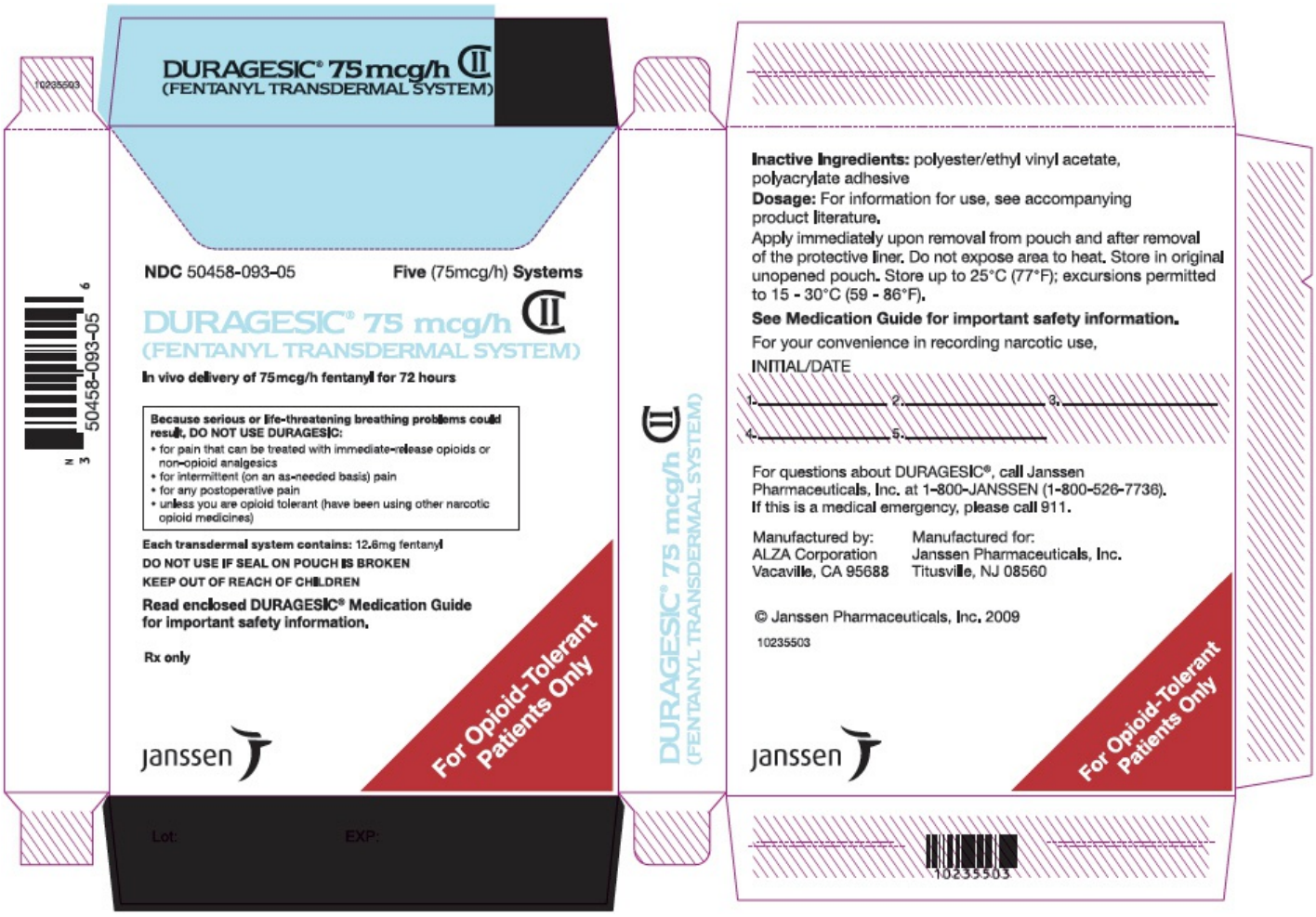
KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

For Opioid-Tolerant Patients Only

Janssen



PRINCIPAL DISPLAY PANEL - 100 mcg/h Patch Carton

NDC 50458-094-05
Five (100mcg/h) **Systems**

DURAGESIC® 100 mcg/h
(FENTANYL TRANSDERMAL SYSTEM)
CII

In vivo delivery of 100mcg/h fentanyl for 72 hours

Because serious or life-threatening breathing problems could result, DO NOT USE DURAGESIC:

- for pain that can be treated with immediate-release opioids or

non-opioid analgesics
- for intermittent (on an as-needed basis) pain
- for any postoperative pain
- unless you are opioid tolerant (have been using other narcotic opioid medicines)

Each transdermal system contains: 16.8mg fentanyl

DO NOT USE IF SEAL ON POUCH IS BROKEN

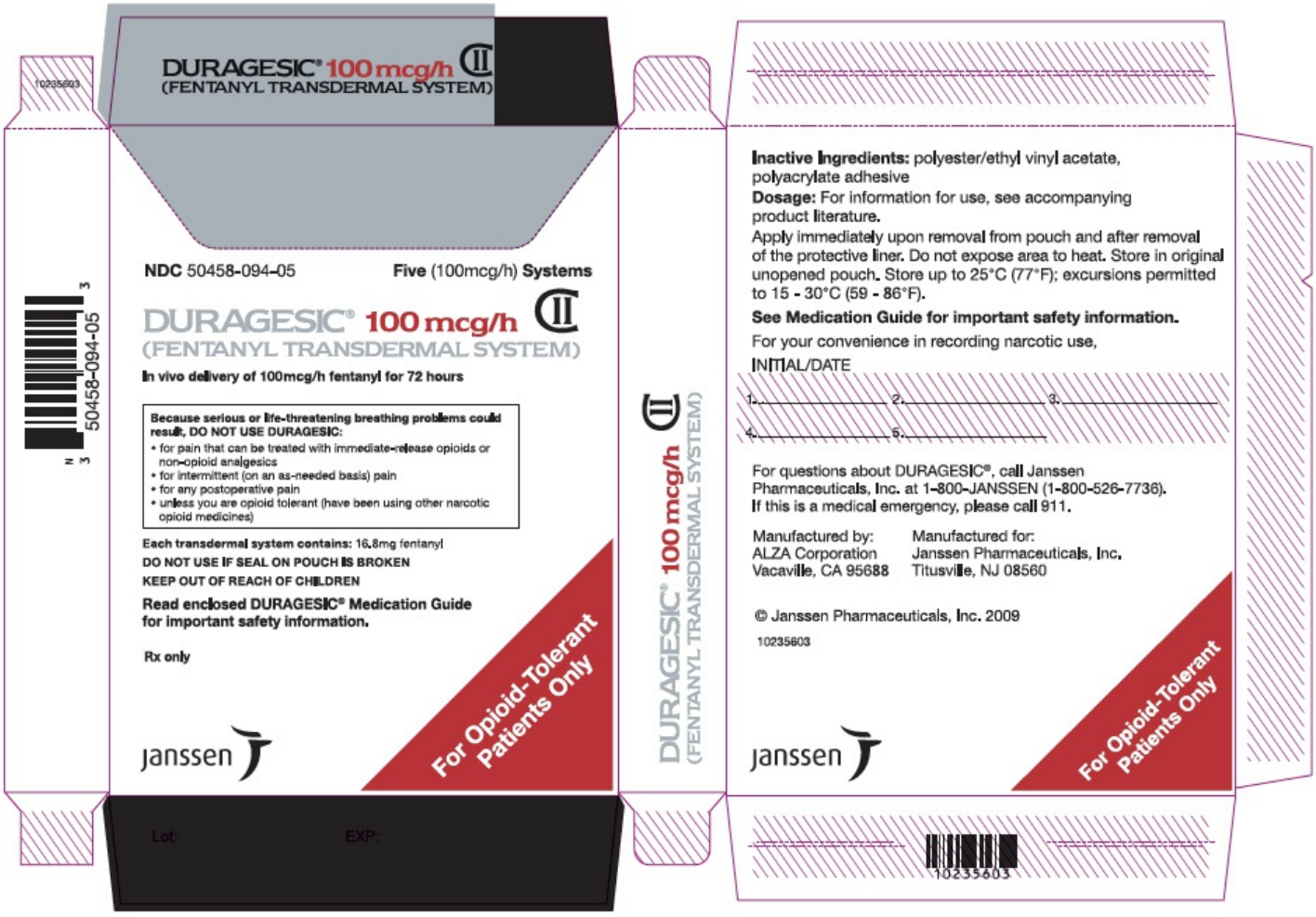
KEEP OUT OF REACH OF CHILDREN

Read enclosed DURAGESIC® Medication Guide for important safety information.

Rx only

For Opioid-Tolerant Patients Only

Janssen



DURAGESIC
fentanyl patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-090
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
fentanyl (UNII: UF599785JZ) (fentanyl - UNII:UF599785JZ)	fentanyl	12.5 ug in 1 h

Inactive Ingredients

Ingredient Name	Strength
Copovidone K25-31 (UNII: D9C330MD8B)	

Product Characteristics

Color	WHITE (Clear, translucent)	**Score**	
Shape	SQUARE	**Size**	53mm
Flavor		**Imprint Code**	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-090-05	5 in 1 BOX		
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019813	08/07/1990	

DURAGESIC

fentanyl patch

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-091
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
fentanyl (UNII: UF599785JZ) (fentanyl - UNII:UF599785JZ)	fentanyl	25 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
Copovidone K25-31 (UNII: D9C330MD8B)	

Product Characteristics			
Color	WHITE (Clear, translucent)	**Score**	
Shape	SQUARE	**Size**	105mm
Flavor		**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:50458-091-05	5 in 1 BOX		
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019813	08/07/1990	

DURAGESIC

fentanyl patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-092
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
fentanyl (UNII: UF599785JZ) (fentanyl - UNII:UF599785JZ)	fentanyl	50 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
Copovidone K25-31 (UNII: D9C330MD8B)	

Product Characteristics			
Color	WHITE (Clear, translucent)	**Score**	
Shape	SQUARE	**Size**	84mm
Flavor		**Imprint Code**	
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:50458-092-05	5 in 1 BOX		
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019813	08/07/1990	

DURAGESIC

fentanyl patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:50458-093
Route of Administration	TRANSDERMAL	**DEA Schedule**	CII

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
fentanyl (UNII: UF599785JZ) (fentanyl - UNII:UF599785JZ)	fentanyl	75 ug in 1 h

Inactive Ingredients	
Ingredient Name	**Strength**
Copovidone K25-31 (UNII: D9C330MD8B)	

Product Characteristics			
Color	WHITE (Clear, translucent)	**Score**	
Shape	SQUARE	**Size**	126mm
Flavor		**Imprint Code**	
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-093-05	5 in 1 BOX		
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information			
Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019813	08/07/1990	

DURAGESIC

fentanyl patch

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50458-094
Route of Administration	TRANSDERMAL	DEA Schedule	CII

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
fentanyl (UNII: UF599785JZ) (fentanyl - UNII:UF599785JZ)	fentanyl	100 ug in 1 h

Inactive Ingredients	
Ingredient Name	Strength
Copovidone K25-31 (UNII: D9C330MD8B)	

Product Characteristics			
Color	WHITE (Clear, translucent)	Score	
Shape	SQUARE	Size	420mm
Flavor		Imprint Code	
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50458-094-05	5 in 1 BOX		
1		1 in 1 POUCH		
1		72 h in 1 PATCH; Type 2: Prefilled Drug Delivery Device/System (syringe, patch, etc.)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA019813	08/07/1990	

Labeler - Janssen Pharmaceuticals, Inc. (063137772)

Establishment

Name	Address	ID/FEI	Business Operations
Alza Corporation		175417641	MANUFACTURE(50458-090, 50458-091, 50458-092, 50458-093, 50458-094) , ANALYSIS(50458-090, 50458-091, 50458-092, 50458-093, 50458-094)

Establishment

Name	Address	ID/FEI	Business Operations
Johnson Matthey Inc.		808176705	API MANUFACTURE(50458-090, 50458-091, 50458-092, 50458-093, 50458-094)

Revised: 8/2014 Janssen Pharmaceuticals, Inc.